Cancer Causes and Control **11**: 451–458, 2000.

Menstrual risk factors and early-onset breast cancer

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Received 1 September 1999; accepted in revised form 19 January 2000

Key words: breast neoplasm, menstruation, risk factors.

Abstract

Objectives: Epidemiologic studies provide evidence for increased breast cancer risk among women with prolonged exposure to endogenous estrogens and progesterone. Menstrual cycle characteristics, such as early menarche, rapid initiation of regular ovulatory cycles, short cycle length, and more days of flow, all potentially contribute to higher cumulative ovarian hormone exposure.
Methods: We assessed the associations between these characteristics and breast cancer risk in a population-based, case–control study of 1505 controls and 1647 newly diagnosed cases, all younger than 45 years of age.
Results: Compared to women with menarche at ≥15 years, we observed some increase in risk for women with younger ages at menarche, although those with very early ages were not at particularly high risk [odds ratio (OR) = 1.5, 95% confidence interval (CI) = 1.1–1.9 for menarche at age 12 and OR = 1.2, 95% CI = 0.9–1.7 for menarche at age ≤10]. Women who reported having regular menstrual cycles within 2 years of menarche were at increased breast cancer risk (OR = 1.7, 95% CI = 1.2–2.3), compared to those never having regular cycles. Stratification by current body mass index revealed slightly stronger associations with menstrual characteristics among thinner women (<22.0 kg/m^2) compared to heavier women (>28.8 kg/m^2).
Conclusions: These findings suggest that future studies should focus on clarifying how the interrelated effects of body size and menstrual factors, such as age at menarche and cycle regularity, contribute to breast cancer etiology.

Introduction

Women who report an earlier age at menarche are at higher risk of breast cancer compared to women with delayed menarche [1, 2]. This association suggests an underlying biologic mechanism of increasing risk with more prolonged exposure to ovarian hormones. Although it has been estimated that breast cancer risk is decreased by about 10% per 2-year delay of menarche [3], the magnitude of effect has varied across studies. In addition, few studies have been large enough to estimate risk among women with very early ages at menarche, *e.g.* at ages 10 or younger.

The variable effect by age at menarche may be explained by the inability of most smaller studies to assess the etiologic heterogeneity of early- and late-onset breast carcinogenesis. Larger studies suggest that stronger associations with early menarche are seen among women with younger ages at breast cancer diagnosis [1], suggesting an etiologic role with early-onset disease. It could be hypothesized that exposure to ovarian hormones earlier in life could serve to initiate and/or promote the accumulation of genetic events that lead to malignancy, and therefore be seen as having a stronger effect with early-onset breast cancer. However, the trend could also be an artifact of better recall of menstrual events among younger women [4, 5].

† This work was carried out while L.M.B. was at the NCI.

Although a number of investigations have evaluated effects of menstrual characteristics, including time of onset of regular cycles, cycle length, and days of flow, only a few have explored the potential joint effects of multiple characteristics, for example age between menarche and cycle regularity [6, 7]. Menstrual characteristics are surrogate measures that may reflect varying levels of estrogens and progesterone, for example a shorter cycle length is thought to infer a longer luteal phase when breast epithelial cell proliferation and estrogen and progesterone are at their highest levels [8, 9]. Varying levels of ovarian hormone exposure may influence breast cell division rates, and thereby breast cancer risk [10–12]. Some investigations have suggested that women with early ages at menarche establish regular menstrual cycles more rapidly than women with later ages at menarche [13–16]. Thus, a collective assessment of menstrual characteristics may provide a clearer picture of the role ovarian hormones play in the etiology of early-onset breast cancer.

In a large, case–control study of younger women, under age 45, we were able to assess the association between very early menarche and breast cancer, as well as its possible interaction with rapid initiation of regular cycles and other menstrual characteristics. With detailed information on traditional risk factors and additional menstrual characteristics, such as cycle length and days of flow, we attempted to identify a menstrual profile most strongly associated with early-onset breast cancer.

Materials and methods

This population-based, case–control study included women newly diagnosed with breast cancer in the two metropolitan areas of Atlanta, Georgia, and Seattle/Puget Sound, Washington, and in five counties of central New Jersey. Study cases include all women under 45 years at the Georgia, Washington, and New Jersey sites with *in situ* or invasive breast cancer diagnosed between 1 May 1990 through 31 December 1992. Cases were identified through frequent monitoring of hospital admissions, surgery, and pathology records, while periodic checks were made against existing cancer registries to ensure complete ascertainment. In addition, hospital records of these patients were abstracted to document details on the clinical and pathologic characteristics of the diagnosed breast cancers. More detailed methods of this study have been previously described [17, 18].

Controls at all sites were identified through random-digit-dialing, using Waksberg's secondary clustered sampling technique [19]. Only telephone numbers assumed to be residential households, based on the three-digit prefix, were included in the sample. A 90.5% response rate to the telephone screener was obtained from the 16,254 residential telephone numbers. Once determined eligible, controls were randomly selected such that they were frequency matched by geographic area and age to the expected distribution of cases.

In-person interviews were conducted in subjects' homes and lasted an average of 71 minutes. Interviewers collected detailed information on demographic factors, reproductive history (including breast-feeding and menstrual characteristics), exogenous hormone use, alcohol consumption, smoking, family history of cancer, and opinions about what might cause breast cancer; in addition, a variety of anthropometric measurements were taken at the time of interview. During the interview, a month-by-month calendar was used to record major events in the woman's life, including oral contraceptive usage and pregnancy history. To collect menstrual factor information, the study participant was first asked her age at menarche and menstrual regularity. The definition of regular menstruation was "when you could usually predict about when they would start." To characterize onset of regular menstrual cycles, we inquired about how periods became regular, for example, "naturally, because of taking birth control pills, or in some other way." In addition, we asked about the usual pattern of cycle length and duration of menstruation in the absence of oral contraceptive use, throughout reproductive life.

Completed interviews were obtained from 2203 of the 2551 eligible cases (86.4%) and 2009 of the 2571 eligible controls (78.1%). Reasons for nonresponse (%cases, %controls) included: physician refusal for interview (5.4%, N/A); participant refusal (6.4%, 18.5%); death (0.4%, 0.2%); illness (0.6%, 0.2%); a move outside of the study area (0.6%, 2.3%); and other miscellaneous reasons (0.2%, 0.8%). Among controls, an overall response rate of 73.4% was achieved (the product of telephone screener and interview response rates). Cases without residential telephones (29 total) were excluded, and data analysis was restricted to women under 45 years of age (1647 cases, 1505 controls). The final sample sizes available for analysis of variables related to menstrual cycle regularity, length, and days of flow were 1535 cases and 1345 controls.

Logistic regression models, as implemented by the statistical package BMDP [20], were used to obtain maximum-likelihood estimates of the odds ratios and associated 95% confidence intervals. The main effects included age at menarche, time until regular menstrual cycles, menstrual cycle length, and days of flow.

Confounding effects of a number of covariates were assessed individually and all together by evaluating the difference in parameter estimates of the main effect between the crude and adjusted models. If a 10% or greater change was detected, then the covariate was retained in the final adjusted model. The covariates of interest were oral contraceptive use (ever, never or use <6 months; never use or <6 months, 6 months to <5 years, 5–9 years, ≥10 years), current body mass index (BMI) by quartiles among controls (<22.0, 22.0–24.6, 24.7–28.8, >28.8 kg/m^2), age (<35, 35–39, 40–44 years), race (white, black, other), smoking history (ever/never), combined parity (nulliparous, 1, 2, 3, ≥4 births) and age at first full-term pregnancy (<25 or ≥25 years), highest level of education (≤ high school, vocational/technical, some college, college graduate, postgraduate), family history of breast cancer (sister and/or mother, neither), breast-feeding (ever/never), weekly alcohol consumption (<1, 1–6.9, 7–13.9, >13.9 drinks), and previous breast biopsy (yes/no).

Heterogeneity of the odds ratio of the menstrual factors and risk of breast cancer was assessed by stratified analyses of potential effect modifiers. Mantel–Haenszel statistics were used to assess statistically significant departure from the null hypothesis of no effect, assuming homogeneity [21]. Then each potential modifier was added to the adjusted model to assess for interaction on the multiplicative scale using the likelihood ratio test, by comparing the model with interaction terms to a reduced model containing the main effects. Next interaction was assessed on the additive scale by creating a common reference group for the main effect and potential modifier and then estimating the joint effects due to combinations of variables. If the joint effect was greater than the sum of the individual effects (after subtracting 1.0 for the common referent group), then interaction was deemed present on the additive scale [22]. The measure used to calculate interaction on the additive scale was the interaction coefficient ratio (ICR) [22]. Confidence intervals for the ICR were calculated to assess the precision of the measure of interaction [23, 24]. Tests for trend were conducted by calculating p-values for the β coefficient in a logistic regression model with the exposure coded as an ordinal variable [25].

Results

Previous reports from this study population have presented the distributions of traditional breast cancer risk factors [17, 18]. Notably, positive associations were found for nulliparity (OR = 2.1, compared with ≥4 births), late age at first birth (OR = 1.4 for ≥30 compared <20 years), race (OR = 1.2 for African-Americans compared to whites), previous breast biopsy (OR = 1.5 for yes *vs.* no), and family history of breast cancer (OR = 2.4 for mother or sister *vs.* neither). Breast cancer risk was not strongly influenced by either duration of breast-feeding (OR = 0.9 for ≥24 months compared to none) or years of education (OR = 0.9 for college graduate compared to high school or less). Body weight was related to breast cancer risk with 35% lower risk among women in the highest quartile of BMI (>28.8 kg/m^2), compared with women in the lowest quartile (<22.0 kg/m^2).

Table 1 presents the distributions of various menstrual characteristics separately for cases and controls. There were virtually no differences between breast cancer cases and controls for mean age at menarche, menstrual cycle length, or days of flow. However, cases were more likely than controls to report ever having regular cycles (95% *vs.* 92%, p-value = 0.001), and to report onset of regular cycles within 2 years of menarche (74% *vs.* 68%, p-value = 0.02). With respect to mode of regular cycling, cases were more likely to report becom-

Table 1. Distribution of menstrual characteristics by case–control status

Menstrual characteristic	Cases	Controls	Test statistics[a]
Age at menarche (years) (mean ± s.d.)	12.4 ± 1.6	12.5 ± 1.5	2.4[b]
Cycle length (days) (mean ± s.d.)	28.1 ± 3.4	28.3 ± 4.0	1.4
Days of flow (mean ± s.d.)	5.2 ± 1.4	5.1 ± 1.4	−1.3
Regular cycles	94.7%	91.7%	10.9[b]
Regular cycle Initiated:			0.7
Naturally	86.3%	82.9%	
After taking oral contraceptives	7.1%	7.6%	
Some other way	1.2%	1.0%	
Regularization in <2 years of menarche	74.0%	68.3%	5.4[b]

[a] t-Test used for continuous variables and Pearson chi-square used for categorical variables.
[b] p-Value <0.05.

ing regular without intervention (86% of cases compared to 83% of controls), while controls were more likely to be irregular even after use of oral contraceptives (2.3% of controls *vs.* 1.5% of cases).

Adjusted odds ratios (ORs), and 95% confidence intervals (CI), for breast cancer and the various menstrual characteristics are presented in Table 2. There was some indication of increased risk among women with earlier ages at menarche (*e.g.* those with menarche at ages 12–13 were at a 40–50% higher risk than those with menarche at ages 15 or older), although subjects with the earliest menarche (≤10) had risks similar to those with late menarche. This association was not affected by adjustment for other breast cancer risk factors, including body size, which has been found elsewhere to be inversely correlated with ages at menarche [26]. Women with regular cycles were at significantly higher risk than those with irregular cycles (OR = 1.6; 95% CI = 1.2–2.1). This association persisted even among women who reported that they had never used oral contraceptives. In addition, women whose periods became regular within 2 years of menarche were at highest risk of breast cancer (OR = 1.7; 95% CI = 1.2–2.3), compared to women who reported never having regular cycles. Only weak associations were found with shorter cycle length (OR = 1.2, 95% CI = 0.8–1.7 for ≤24 *vs.* >30-day cycles) and more days of flow (OR = 1.2, 95% CI = 0.9–1.6 for >6 *vs.* <4 days).

Table 2. Odds ratios[a] (OR) and confidence intervals (CI) for the association between breast cancer and various menstrual factors among women younger than 45 years of age

Risk factor	Cases[b]	Controls	OR	95% CI
Age at menarche (years)[c]				
≥15	126	148	1.0	–
14	167	158	1.2	0.8–1.7
13	443	446	1.4	1.0–1.5
12	512	402	1.5	1.1–1.9
11	258	218	1.1	0.9–1.5
≤10	139	131	1.2	0.9–1.7
Ever regular				
No	85	122	1.0	–
Yes	1532	1363	1.6	1.2–2.1
Years from menarche to regular menstrual cycles				
Never Regular	85	122	1.0	–
≥5	168	160	1.5	1.1–2.1
2–4	168	189	1.3	0.9–1.8
<2	1196	1014	1.7	1.2–2.3
Cycle length (days)[d]				
>30	138	144	1.0	–
28–30	1073	926	1.2	0.9–1.5
25–27	195	169	1.2	0.9–1.6
≤24	117	98	1.2	0.8–1.7
Days of flow[d]				
<4	136	130	1.0	–
4–6	1091	972	1.0	0.8–1.4
>6	307	241	1.2	0.9–1.6

[a] Adjusted for age, study site, race, combined age at first full-term pregnancy and parity, and family history of breast cancer.

[b] For some variables, the number of observations does not equal 3152 (1647 cases and 1505 controls) due to missing data.

[c] Test for trend ($p = 0.0483$).

[d] Includes only women who reported ever having regular menstrual cycles.

We explored interrelationships between menstrual characteristics, among control women (Tables 3a and 3b). We found no evidence of a relationship between age at menarche and years to regularity. A slight, increasing trend in mean cycle length with age at menarche was seen, although it was not statistically significant. Increasing variability in cycle length (*i.e.* increasing standard deviation) with later age at menarche was indicated. There was evidence for a small inverse correlation between age at menarche and days of flow. A U-shaped correlation was detected between cycle length and mean interval to regularity, with women who reported shorter (≤24 days) or longer (>30 days) cycle length having, on average, a longer interval between menarche and regular cycles. There was no correlation between cycle length and mean days of flow. The Spearman rank correlation coefficients (r_s) for all these comparisons ranged from $r_s = -0.05$ to 0.06.

In further analyses it was determined that a greater proportion of women with younger age at menarche (≤11 years), particularly among controls, never had regular menstrual cycles (cases = 6%, controls = 10%), compared to women who were 12–13 years old at menarche (cases = 5%, controls = 6%). Similar results were observed when restricting analyses to women who reported menarche at ≤10 years. Thus, when age at menarche associations were examined according to the interval at which periods became regularized (Table 4), age at menarche appeared to be more of a risk factor in those with regular cycles. However, of note was that extended intervals until regularization of menstrual periods was a risk factor for all ages at menarche, even subjects with the earliest menarcheal ages. Other potential interactive effects of menstrual characteristics were also examined, including joint effects of menstrual ages, cycle lengths and days of flow. These cross-classifications of risk showed no further discriminations of risk.

Given previous observations that obese women are more likely to experience early ages at menarche and anovulatory cycles [26, 27], we evaluated associations with the menstrual characteristics according to body mass index (BMI) (Table 5). Similar to the findings of

Table 3. Selected menstrual characteristics (mean ± standard deviation) by age at menarche and cycle length among control women
a

Menstrual Characteristics	Age at menarche (years)			
	≤11	12	13	≥14
Mean interval to regular cycles (years)	1.7 ± 3.6	1.3 ± 3.1	1.9 ± 4.1	1.7 ± 3.5
Mean cycle length (days)	28.1 ± 2.7	28.1 ± 2.9	28.5 ± 3.5	28.7 ± 6.3
Mean days of flow	5.3 ± 1.7	5.1 ± 1.3	5.0 ± 1.4	5.1 ± 1.3

b

Menstrual characteristics	Cycle length (days)			
	≤24	25–27	28–30	> 30
Mean interval to regular cycles (years)	2.6 ± 4.1	1.3 ± 2.7	1.3 ± 3.2	2.5 ± 4.9
Mean days of flow	5.2 ± 1.4	5.0 ± 1.3	5.1 ± 1.4	5.2 ± 1.7

Table 4. Joint effects[a] (ORs and 95% CIs) of age at menarche and interval to regular cycles on breast cancer risk among women younger than 45 years of age

Age at menarche (years)	Years to regular cycles		
	Never regular	≥2	< 2
≥14	1.0	1.5 (0.8–3.0)	2.0 (1.1–3.8)
13	1.5 (0.7–3.3)	1.5 (0.8–3.0)	2.0 (1.1–3.7)
12	1.7 (0.8–3.9)	2.3 (1.2–4.5)	2.4 (1.3–4.5)
≤11	1.1 (0.5–2.5)	2.0 (1.0–3.8)	2.3 (1.3–4.3)

[a] Adjusted for age, study site, race, combined parity and age at first full-term pregnancy, and family history of breast cancer.

most epidemiologic studies of early-onset breast cancer, the thinnest women (< 22.0 kg/m^2) were at increased risk of breast cancer, regardless of their menstrual characteristics (Table 5). Regular cycles were a slightly stronger risk factor among heavier women, although the interaction between BMI and cycle regularity was not statistically significant. In contrast, associations with age at menarche and days of flow were stronger risk factors in thinner rather than heavier women, although chance could have explained this variation. Departure from the expected purely additive effects was present for the effects of ever regularity [ICR = 0.4, 95% CI = (−0.2–

Table 5. Odds ratios for breast cancer associated with menstrual characteristics after stratification by body mass index[a]

Menstrual characteristics	Body mass index (kg/m^2)			
	> 28.8	24.7–28.8	22.0–24.6	< 22.0
Ever regular				
No	1.0	1.3 (0.6–2.9)	1.4 (0.6–3.1)	1.9 (0.8–4.1)
Yes	1.9 (1.1–3.4)	2.2 (1.3–3.9)	2.0 (1.1–3.5)	2.5 (1.4–4.4)
Age at menarche (years)				
≥14	1.0	1.6 (0.9–2.8)	1.3 (0.8–2.2)	1.3 (0.7–2.0)
13	1.0 (0.6–1.8)	1.2 (0.7–2.0)	1.2 (0.7–2.0)	1.5 (0.9–2.5)
12	1.5 (0.9–2.5)	1.4 (0.9–2.4)	1.4 (0.8–2.4)	2.3 (1.4–3.8)
≤11	1.2 (0.7–2.0)	1.6 (1.0–2.7)	1.4 (0.8–2.4)	2.1 (1.2–3.7)
Cycle length (days)[b]				
> 30	1.0	1.2 (0.7–2.2)	1.1 (0.6–2.0)	1.5 (0.9–2.6)
28–30	1.2 (0.8–1.8)	1.4 (0.9–2.0)	1.2 (0.8–1.7)	1.5 (1.1–2.3)
25–27	1.2 (0.6–2.2)	1.3 (0.7–2.2)	1.3 (0.8–2.1)	1.7 (1.0–2.9)
≤24	0.9 (0.4–1.7)	1.9 (1.0–3.7)	1.4 (0.7–2.6)	1.3 (0.7–2.6)
Days of flow[b]				
< 4	1.0	0.7 (0.4–1.1)	1.3 (0.8–2.0)	0.7 (0.4–1.2)
4–6	0.8 (0.6–1.1)	1.1 (0.8–1.4)	0.8 (0.6–1.0)	1.1 (0.8–1.4)
> 6	1.0 (0.7–1.5)	1.0 (0.8–1.4)	1.1 (0.8–1.5)	1.2 (0.9–1.6)

[a] Odds ratios are adjusted for age, study site, race, combined parity and age at first full-term pregnancy, and family history of breast cancer.
[b] Includes only women who reported ever having regular menstrual cycles.

1.0)], age at menarche [ICR = 0.8 (0.1–1.4)], and days of flow [ICR = 0.5, (−0.02–1.1), where ICR = 0.6 indicates no departure from expected additive effects.

Discussion

In this study of women under 45 years of age, various menstrual characteristics, including cycle regularity and earlier age at menarche, were found to be associated with modest increases in a woman's risk of breast cancer. In addition, a short interval of < 2 years from menarche to cycle regularity was positively associated with breast cancer irrespective of age at menarche, while other self-reported cycle characteristics, such as cycle length and days of flow, showed only minimal differences between cases and controls. These associations, however, appeared to be dependent on body size, with stronger effects of age at menarche and a distinctive relationship with days of flow observed among thin women.

The bulk of the epidemiologic literature supports a modest association between earlier age at menarche (< 12 years) and increased breast cancer risk [1]. In our study of early-onset breast cancer, breast cancer risk increased with earlier ages at menarche, although subjects with very early ages (prior to age 12) were at an attenuated risk. This curtailment of risk among women with very early ages at menarche was also observed in a recent population-based study of premenopausal breast cancer [28]. It has been suggested that this may reflect a propensity of women with early menarche to have characteristics that would otherwise predispose to a low risk of early-onset breast cancer. One suggested factor is adult body size, a factor found in a recent cohort study to be highly correlated with earlier onset of puberty (as measured by age at menarche, breast development, presence of pubic and axillary hair) [26]. However, in the present study, we did not find this to be the explanation for the attenuation in risk with early ages at menarche. Instead, women with young ages at menarche appeared more likely not to establish regular menstrual cycles, a strong predictor of subsequent breast cancer risk in this, as well as other, investigations [4, 29, 30].

In support of other epidemiologic studies [1, 4], women who had a shorter interval from menarche to initiation of regular cycles (< 2 years) were at higher risk of breast cancer than women who never had regular menstrual cycles. Some investigators have suggested that women with early ages at menarche have menstrual periods that are quickly regularized and that these women are at highest risk of breast cancer [15, 31], while others have found that these factors increase risk independently [7, 32]. The inconsistency between studies reporting on the combined effects of early menarche and short interval to regular cycles may be due, in part, to the small number of women who report never having regular cycles. We also found that women reporting early ages at menarche and a shorter interval to regular cycles were at highest risk of breast cancer; however, the joint effect of these two menstrual characteristics was approximately equal to the sum of their individual effects. In fact, our data suggest that menarche appears to be more of a risk factor in those with regular cycles.

Previous investigations have reported that thin women are at higher risk of early-onset breast cancer, compared to heavier women [3, 33]. Hypotheses used to explain this inverse association include less effective tumor detection [34, 35], diminished cellular proliferation due to altered endocrine function among heavier women [5], and increased frequency of anovulation, hence less cumulative exposure to ovarian hormones [27]. Our results suggest that stronger associations between breast cancer and certain menstrual characteristics may occur among thinner women. Although formal assessment of interaction revealed slightly greater than expected joint effects between BMI and both age at menarche and longer days of flow, caution is warranted due to limited statistical precision in estimating the individual effects. Nevertheless, these results provide some support for a hypothesis involving the effects of BMI, in that heavier women are more likely to have later initiation of ovulatory cycles which are thought to decrease exposure to ovarian hormones, thereby decreasing risk of early-onset breast cancer. The specific mechanisms of this trend have yet to be fully explored.

We are limited in our ability to address the influence of ovarian hormones on breast cancer risk, because we could not directly determine when regular ovulation was established. Although we relied on self-reported data, the recall of menstrual characteristics such as age at menarche and cycle regularity have been determined to have moderate accuracy in a cohort of women 25–64 years old [36]. We asked study participants to recall the age at which initiation of regular cycles occurred, but were unable to assess whether the regular cycling persisted throughout the woman's reproductive life. Menstrual cycles are influenced by many life events, such as vigorous exercise, diet, and history of pregnancy [37]. Our focus on initiation of regular cycles (ever/never), without inquiry into the pattern of regularity throughout reproductive years, may have introduced non-differential misclassification by case–control status,

thereby potentially underestimating the risk associated with regular cycles [38]. In a recent study of breast cancer, women were asked about cycle regularity at three age intervals, 18–34 years, 35–44 years, and 45–54 years. Women who reported a longer time until regular cycling were, on average, more likely to report irregular cycling throughout young adulthood (between ages 18 and 34 years) [7]. Therefore our one-time assessment of cycle regularity may be reasonably representative of patterns throughout a woman's life.

Results from prospective studies have suggested a correlation between the establishment of regular menstrual cycles and the start of ovulatory cycles [39, 40]. Ovulatory cycles are characterized by a pattern of ovarian hormone fluctuations that varies during the follicular and luteal phases of the menstrual cycle. Laboratory studies have suggested that elevated breast cell division rates result from these characteristic hormonal fluctuations, which might increase the probability of genetic mutation [41, 42]. This mechanism may explain the increased risk of breast cancer among women with rapid regularization of menstrual cycles, if indeed it is a surrogate for earlier ovulatory cycling.

In this large study of young women, we continue to find support for the modest association between menstrual characteristics, such as earlier age at menarche ($\leq$12 years *vs.* $\geq$15 years) and shorter interval to regular cycles ($<$2 years *vs.* $\geq$5 years), with breast cancer risk. If the self-report of regular cycles is an accurate measure for ovulation, then our findings suggest that combined exposure to estrogens along with progesterone early in the reproductive years may play an important role in breast carcinogenesis. However, the mechanisms that are involved in hormone production are complex. For example, genetic heterogeneity at the CYP17 locus [43], as well as lifestyle influences such as diet and exercise [37, 44, 45], can influence hormone levels. We recommend that future research focus on elucidating mechanisms that involve hormone exposure and the influence of body mass, especially early in life, in order to make specific public health recommendations to subsequent generations of women that would ensure a reduction in their risk of breast cancer.

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